UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/432,906	11/02/1999	ALEXANDER BAGUISI	1322.1032-001	1763

21005 7590 11/28/2001

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.
530 VIRGINIA ROAD
P.O. BOX 9133
CONCORD, MA 01742-9133

EXAMINER	
CROUCH, DEBORAH	
ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 11/28/2001

16

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/432,906	BAGUISI ET AL.	
	Examiner	Art Unit	
	Deborah Crouch	1632	

-- Th MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 August 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4,5,7-9,11-17,19-26 and 28-59* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,5,7-9,11-17,19-26 and 28-59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☒ Interview Summary (PTO-413) Paper No(s). *15* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Claims 1-38 are pending and subject to examination in this office action.

Benefit of priority for claims 31-38 to 60/106,728, filed Nov. 2, 1998 is denied. The subject matter of the claims, enucleation of oocytes having meiotic spindle apparatus, is not disclosed in the '728 specification. The only enucleation found is the enucleation of MII oocytes by cytochalasin B (page 41, parag. 2). There is no protocols specifically given for oocytes with a mitotic spindle apparatus such as telophase nuclei. Applicant is requested to point to page and line number for any support over-looked by the examiner. Thus for claims 31-38, a priority date of April 26, 1999 is given.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-37 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the methods of cloning an animal, methods of cloning a transgenic animals, methods of producing a protein or methods of producing a heterologous protein comprising introducing a nucleus from an activated donor cell into an activated oocyte of the same species in telophase II of meiosis form a non-human mammalian reconstructed embryo, activating the reconstructed embryo and transferring the embryo to a recipient mammal of the same species to produce a non-human mammal, does not reasonably provide enablement for the methods as claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims.

Claims 1-37 are drawn to methods of producing a cloned non-human mammal comprising introducing a genome from a non-human mammalian somatic cell into a naturally-matured oocyte which is in a telophase stage of meiotic cell division to form a

reconstructed embryo and allowing the reconstructed embryo to develop into a mammal thereby providing a non-human mammal.

The designation that the oocyte must be in telophase II is critical to the invention because at this stage the MPF level in the oocyte is low as is needed for successful nuclear transfer resulting in the birth of a mammal (WO 97/07668, Campbell, page 4, lines 5-7). There is no evidence of record, or in the art, that oocytes in telophase I would provide the correct environment to reprogram the donor nucleus. It is known in the art that exposure of the donor nucleus to recipient ooplasm is critical for reprogramming events to occur (W0 97/07668, Campbell, page 12, lines 22-28). As an oocyte in telophase I in nature would not ever be a recipient for sperm, it is unlikely that telophase I ooplasm has the environment necessary to induce post-fertilization events that would reprogram the donor nucleus and lead to the development of a term mammal. Likewise, there is no evidence that an oocyte of a different mammalian species would provide the correct environment to foster development of a term mammal. While the art has shown that cross-species nuclear transfer will result in the production of a cross-species embryo, there has not been any showing that the embryo can develop and sustain itself in a foreign environment. For example, the trophoblast of the embryo contributes the formation the placenta. The placenta thus would be composed of proteins from the species of the embryo, and also composed of proteins from the foster mother species. It is very likely that the maternal immune system would recognize the placenta as being "foreign" and reject the embryo causing a pre-term loss. This is documented in the formation of "geeps" goat x sheep hybrid embryos, where term births were correlated to the degree that the placenta was formed of maternal tissues (Meinecke-Tillman, page 638, col. 1, parag. 2, lines 1-9). The specification provides no guidance as to overcoming the maternal rejection of a hybrid placenta, and such is critical to the implementation of the claims. Furthermore, activation of the embryo is a critical step to the development of the term mammal. Without activation, the reconstructed embryo does not

develop. It is noted that in the specific examples, the oocyte is in telophase II, the recipient oocyte, donor nucleus and recipient female are all of the same species, and that prior to transfer to the female the reconstructed embryo is activated. The specification through discussion and the working examples only provides guidance for this scenario. Thus, it would require an undue amount of experimentation to implement the invention as claimed.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-5,7-9,11,14,15,19 and 20 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by WO 97/07668 published March 6, 1997 (Campbell).

Campbell teaches the production if a nuclear transfer embryo by the nuclear transfer of a G1 somatic cell nucleus by fusion of the nucleus with an activated enucleated oocyte after the disappearance of MPF activity and that the oocyte can be in MII prior to activation (page 4, lines 5-7), and the production of cloned non-human mammals by the same method followed by transfer of the reconstructed embryo to a surrogate mother (page 15, lines 23-27). Campbell teaches that the nucleus may be genetically modified to contain a DNA sequence of interest (page 7, lines 4-14). Campbell further discloses that the cell can be a fetal fibroblast (page 26, lines 4-6), that the nucleus can be introduced into the oocyte by microinjection (page 11, lines 28-32) and enucleation by aspiration and x-irradiation (page 10, lines 1-16). Thus, Campbell clearly anticipates the invention of claims 1-5,7-9,11,14,15, 19 and 20.

Claims 31,32 and 34 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Bordignon et al (1998) Molec. Reprod. Devel. 49, 29-36.

Bordignon et al teach the enucleation of telophase nuclei, which have a mitotic spindle apparatus, by incubating the nuclei in cytochalasin B (page 31, col. 1, parag. 1, line 3-6; parag. 2, lines 1-15; and col. 3, parag. 1, line 1 to page 32, line 5). Both the meiotic spindle apparatus and chromosomes were destabilized as evidenced by fragmented chromatin in the first polar body (page 31, fig.1, legend). The media surrounding was altered as evidenced by the inclusion of Hoechst 33342 (page 31, col. 1, parag. 2, lines 8-11). Thus, Bordignon clearly anticipates the claimed invention.

Claims 35,36 and 38 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Bordignon et al (1998) Molec. Reprod. Devel. 49, 29-36.

Bordignon et al teach the enucleation of telophase nuclei, which have a mitotic spindle apparatus, by incubating the nuclei in cytochalasin B (page 31, col. 1, parag. 1, line 3-6; parag. 2, lines 1-15; and col. 3, parag. 1, line 1 to page 32, line 5). Both the meiotic spindle apparatus and chromosomes were destabilized as evidenced by fragmented chromatin in the first polar body (page 31, fig.1, legend). The oocytes were activated by exposure to ethanol (page 30, col. 2, parag. 1, lines 1-11). Thus Bordignon clear anticipates the claimed invention.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1,6,8,10,11 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 97/07668 published March 6, 1997 (Campbell) in view of Wu et al (1997) Biol. Reprod. 56, 253-259.

Campbell teaches the production of cloned non-human mammals by the nuclear transfer of a G1 somatic cell nucleus by fusion of the nucleus with an activated enucleated

oocyte after the disappearance of MPF activity (page 4, lines 5-7), followed by transfer of the reconstructed embryo to a surrogate mother (15, 23-27). Campbell teaches that the nucleus may be genetically modified to contain a DNA sequence of interest (page 7, lines 4-14). However, Wu does not teach the recipient oocyte to be metaphase I, anaphase I, anaphase II or telophase II. Wu supplements Campbell by stating that at the anaphase/telophase stage of meiosis, oocytes have an abrupt reduction in MPF activity (page 253, abs, line 10-14). Thus at the time of the instant invention it would have been obvious to the ordinary artisan to modify the method of Campbell by using a telophase II oocyte which has low levels of MPF, as taught by Wu, given the motivation of Campbell that a suitable recipient oocyte is one that is preactivated having low levels of MPF (page 4, lines 5-7). Thus, at the time of the instant invention it would have been obvious to the ordinary artisan to modify the teachings of Campbell and use as a recipient oocyte one that was in anaphase or telophase stage of meiosis. A reasonable expectation of success is provided by the combination of prior art.

Claims 11-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 97/07668 published March 6, 1997 (Campbell) in view of U.S. Patent 5,945,577 issued August 31, 1999 (efd January 10, 1997)(Stice).

Campbell teaches the production of a nuclear transfer embryo by the nuclear transfer of a G1 somatic cell nucleus by fusion of the nucleus with an activated enucleated oocyte after the disappearance of MPF activity (page 4, lines 5-7). However, Campbell does not teach activation by exposing the oocyte to increase calcium levels or the inclusion of decreasing phosphorylation in the oocyte. Stice supplements Campbell in teaching Stice teaches oocyte activation by elevating the number of calcium ions (col. 10, lines 47-50), and the reduction of phosphorylation (col. 10, lines 57-59). Motivation is provided by Stice teaching that these are methods successfully resulted in a cloned mammal (col. 17, lines 12-16 and lines 35-50). Thus at the time of the instant invention, it would have been obvious to the ordinary artisan to modify the method of Campbell by activating the oocyte using incubating the oocyte in an

increase concentration of calcium by incubation with a calcium ionophore and incubation in the presence of DMAP, a phosphorylation inhibitor as taught by Stice.

Claims 21-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 97/07668 published March 6, 1997 (Campbell) in view of Wu et al (1997) Biol. Reprod. 56, 253-259 and Ebert et al (1991) Bio/Technology 9, 835-838.

Campbell teaches the production if a nuclear transfer embryo by the nuclear transfer of a G1 somatic cell nucleus by fusion of the nucleus with an activated enucleated oocyte after the disappearance of MPF activity (page 4, lines 5-7), and the production of cloned non-human mammals by the same method followed by transfer of the reconstructed embryo to a surrogate mother (page 15, lines 23-27). Campbell teaches that the nucleus may be genetically modified to contain a DNA sequence of interest (page 7, lines 4-14). Campbell further discloses that the method disclosed will produce cloned goats (page 5, lines 20-24). However, Campbell does not teach using an oocyte in the telophase of meiosis. In this regard Campbell teaches that for successful cloning, the recipient oocyte needs to have low levels of maturation promoting factor (MPF). Wu supplements the teachings of Campbell by stating that at the anaphase/telophase stage of meiosis, oocytes have an abrupt reduction in MPF activity (page 253, abs, line 10-14). Campbell does not teach the use as nuclear donor, a cell whose genome comprises a DNA sequence encoding an human protein operatively linked to a milk-specific promoter, induction of a female mammal to lactated, or recovering a product from the milk of the female. However, Ebert supplements Campbell in teaching the production of human tPA in the milk of goats, where the goat's genome comprises a DNA sequence encoding human tPA operably linked to a mouse WAP promoter (836, 2, 1 and 837, 1, 3, 1-8). Ebert additionally teaches breeding the transgenic goat (page 838, col. 1, lines 17-18). Thus at the time of the instant invention it would have been obvious to the ordinary artisan to modify the method of Campbell by using a telophase II oocyte which has low levels of MPF, as taught by Wu, given the motivation of Campbell that the recipient oocyte needs to

have low levels of MPF, and using as nuclear donor the a cell from a transgenic goat taught by Ebert. The isolation of goat cells was well within the scope of skill of the ordinary artisan at the time of the instant invention, given the motivation of Campbell that their method is "equally applicable in the production of transgenic ... animals" (page 5, lines 30-31). A reasonable expectation of success is provided by the combination of prior art. Any protein that is immuno-detectable as is the tPA of Ebert's goats is also recoverable by elution methodology known to the ordinary artisan at the time of the instant invention.

Claims 31,33,35 and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bordignon et al (1998) Molec. Reprod. Devel. 49, 29-36.

Bordignon et al teach the enucleation of telophase nuclei, which have a mitotic spindle apparatus, by incubating the nuclei in cytochalasin B (page 31, col. 1, parag. 1, line 3-6; parag. 2, lines 1-15; and col. 3, parag. 1, line 1 to page 32, line 5). Both the meiotic spindle apparatus and chromosomes were destabilized as evidenced by fragmented chromatin in the first polar body (page 31, fig.1, legend). The oocytes were activated by exposure to ethanol (page 30, col. 2, parag. 1, lines 1-11). However, Bordignon does not teach destabilization of the meiotic spindle apparatus using demecolcine, nocodazole, colchicine or paclitaxel. The art at the time of filing taught that each of these compounds destabilized the mitotic spindle apparatus by depolymerizing the tubulin component of microtubles comprising the apparatus. Thus at the time of the instant invention, it would have been obvious to the ordinary artisan to substitute any tubulin destabilizing agent for cytochalasin B which functions to destabilize chromosomes and centrioles by destabilizing actin of microfilaments. Motivation is provided by Bordignon stating that their method provides for enucleation without the use of DNA strains or UV irradiation with a result of great blastocyst achievement (page 34, col. 1, parag. 1). There is sufficient motivation and teachings in the prior art to provide a reasonable expectation of success.

Claims 11,16 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 97/07668 published March 6, 1997 (Campbell).

Campbell teaches the production of cloned non-human mammals by the nuclear transfer of a G1 somatic cell nucleus by fusion of the nucleus with an activated enucleated oocyte after the disappearance of MPF activity (page 4, lines 5-7), followed by transfer of the reconstructed embryo to a surrogate mother (15, 23-27). Campbell teaches that the nucleus may be genetically modified to contain a DNA sequence of interest (page 7, lines 4-14). However, Campbell does not teach a method of culture by first serum starvation of the cells followed by growth at normal serum concentrations. The art at the time of filing taught that nutrient depravation followed by nutrient supplementation was a means through which to achieve cell cycle synchrozination. Thus, at the time of the instant invention it would have been obvious to the ordinary artisan to modify the teachings of Campbell and a synchronous cell culture. Absent results to the contrary the culture conditions of donor cells is obvious given the teachings of Campbell that "there is no significant limitation on the cell that can be used in nuclear donors" (page 8, lines 13-15). Thus, there is sufficient teachings and motivation in the prior art to provide a reasonable expectation of success.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah Crouch, Ph.D. whose telephone number is (703) 308-1126. The examiner's SPE is Karen Hauda, whose telephone number is (703) 305-6608.

Any inquiry of a general nature or relating to the status of this application should be directed to the Art Unit Patent Analyst, Kay Pinkney, whose telephone number is (703) 305-3553.

The fax number is (703) 308-4242.

Dr. D. Crouch
November 19, 2001